REMARKS

Claims 1-14, 16, 18-20, 22-31, 38-66, 68 and 70-95 are currently pending. Applicants have amended claims 1 and 53 to recite the subject matter of former claims 17 and 69, respectively. Claims 18, 19 and 70 have been amended to correct dependencies based on amendments to claims 1 and 53. Applicants have cancelled claims 15, 17, 67 and 69 without waiver of right to claim this subject matter in one or more continuing applications claiming priority herefrom under 35 U.S.C. § 120. No new matter has been added.

Applicants have submitted an Information Disclosure Statement with this response and ask that the Examiner consider and initial the enclosed Form PTO/SB/08a with the next Office Action.

Rejections under 35 U.S.C. § 103:

(a) Claims 1-20, 22-31, 50, 53-80 and 93 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Freund *et al.* (DE 19653969 as evidenced by US 2001/0008632). To the extent this rejection might still be applied to the claims as presently amended in this application, applicants respectfully traverse.

To establish *prima facie* obviousness of a claimed invention, "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Furthermore, "[s]ection 103 forbids issuance of a patent when the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which [the] subject matter pertains." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007).

In the presently claimed invention, the subject matter as a whole was not obvious in view of Freund *et al.* at the time the invention was made. For example, the Office concedes that the pH range of between 2.0 and 3.0 was not taught by Freund *et al.* Similarly, the reduction in spray anomalies with low levels of edetic acid or edetic acid salt was not taught by Freund *et al.* *See,* Freund *et al.*, discussed in the specification on page 3, line 19, to page 4, line 2 (US 2001/0008632 claims priority to WO 98/27959 or PCT/EP97/07062). Furthermore, in Table 1 on page 3 of Freund *et al.*, a concentration of $\geq$ 50 mg/100 mL of

EDTA in an ipratropium bromide solution yielded "0" spray anomalies as compared to tests run at lower levels of EDTA having between 2-6 spray anomalies. According to MPEP 2144.05 (III), a *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *See, In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997). Without teaching a pH range of 2.0-3.0 and amount of edetic acid or edetic acid salt greater than 0 and up to 25 mg/100 mL, Freund *et al.* does not teach the subject matter as whole and thus, lacks the basis for an obviousness rejection.

The Office states that Freund *et al.* teaches Na-EDTA between 10 and 100 mg/100 mL. However, the overlapping range taught by Freund *et al.* fails to render obvious the claimed range of greater than 0 and up to 25 mg/100 mL of EDTA or salt of EDTA in the present application. According to MPEP 2144.05(III), applicants can overcome a *prima facie* case of obviousness based on overlapping ranges by showing the criticality and unexpected results of the claimed range. Applicants provide data to demonstrate these results (see attachment accompanying this response). If necessary, applicants will provide this data in declaration form upon request of the Examiner.

For all of the above reasons, applicants request reconsideration and withdrawal of this rejection.

(b) Claims 1-20, 22-30, 50, 53-80 and 93 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Bozung *et al.* (DE 19921693 as evidenced by US patent 6,433,027). Applicants respectfully traverse.

In the present application, the subject matter as a whole was not obvious at the time the invention was made. Bozung *et al.* does not disclose the invention as recited in pending claims, specifically with regard to the stability of tiotropium salts in the pH range of 2.0-3.0, respectively. In fact, Bozung *et al.* teaches in one instance (see Table on column 7, lines 20-31) that the pH of its formulation is at a pH of about 3.4. Moreover, Bozung *et al.* is silent with respect to the specific dependence of tiotropium salt stability on pH and provides no motivation to leave the disclosed pH range of about 3.4. In contrast, the present claims teach that the pharmaceutical preparation of a tiotropium salt has a preferred lower pH limit of 2.0 and an upper pH limit of 3.0.

For this reason, along with those provided in part (a), applicants request reconsideration and withdrawal of this rejection.

(c) Claims 1-18, 20, 22-26, 28-31, 50, 53-69, 71-76, 78-80 and 93 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Jager *et al.* (WO 9413262). Applicants respectfully traverse.

The Office acknowledges that Jager *et al.* does not exemplify a formulation comprising tiotropium bromide, a solvent and an acid, where the formulation has a pH range of 2.0-3.0 but argues that Jager *et al.* provides sufficient disclosure to one of ordinary skill in the art to use the formulations as claimed. Based on the claim amendments and arguments made herein, applicants request reconsideration and withdrawal of this rejection.

(d) Claims 38-49, 51, 52, 81-92, 94 and 95 stand rejected as being unpatentable over Freund *et al.* or alternatively over Jager *et al.* as applied to claims listed above, and further in view of Weston *et al.* (WO 9114468). Applicants respectfully traverse.

Based on the claim amendments and arguments made herein, applicants request reconsideration and withdrawal of this rejection.

Obviousness-type Double Patenting:

Claims 1-20, 22-31 and 38-95 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatetnable over claims of copending applications:

(1) 11/068,134 (US 20050147564);

(2) 10/392,558 (US 20040019073);

(3) 11/267,354 (US 20060057074); and

(4) 11/006,940 (US 20050148562).

According to MPEP 804(I)(B)(1), "if a provisional nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer."

All of the above-listed copending applications were filed after the earliest effective filing date of the present application and qualify as "later-filed" applications. Furthermore, the double patenting rejections are the only remaining rejections in this application. Thus, according to the MPEP provision above, terminal disclaimers are not necessary for allowance

of the present claims. Applicants believe that the double-patenting rejections are rendered moot and withdrawal of the same is respectfully requested.

In view of the above remarks, applicants respectfully submit that this application is now in condition for allowance and earnestly request such action.

If any points remain at issue which can best be resolved by way of a telephonic or personal interview, the Examiner is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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ATTACHMENT: Experimental findings concerning spray quality of formulations

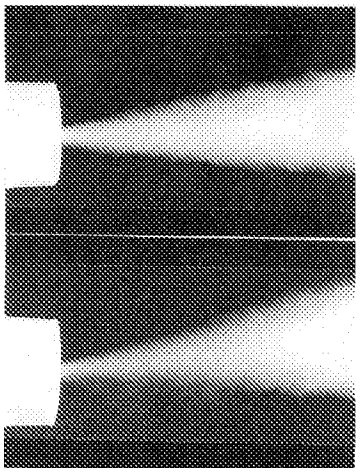
I. Composition of the investigated solutions:

Tiotropium	NaEDTA	BACl	Purified water ad	pH value
0.099 mg	50 mg	10 mg	100 g	2.7
				3.0
				3.1
				3.2
	25 mg			2.7
				2.8
				3.0
				3.1
				3.2
	10 mg			2.7
				2.8
				3.0
				3.1
				3.2
	0 mg			2.7
				3.3

The dosage 0.099mg relates to tiotropium. 1 mg tiotropium corresponds to 1.2495 mg tiotropium bromide;

"BACl" is Benzalkonium chloride;

II. Determination of spray quality:
For assessment of the spray quality the devices were sprayed under a cold light lamp over black paper into a vent. The evaluation was performed visually. The following picture describes a spray generated normally:



III. Results:

The following table gives an overview of actuations that were to be classified as sprays with deviations from the typical spray pattern in dependency from the chosen formulation:

pH value	NaEDTA [mg/100g]	Sprays with deviation			
		Devices		Actuations	
		abs.	rel. [%]	abs.	rel. [%]
2.7	0	0	0	0	0
	10	0	0	0	0
	25	1	2.6	1	0.01
	50	28	70.0	2667	17.10
2.8	10	0	0	0	0
	25	2	5.0	11	0.07
3.0	10	1	2.5	1	0.01
	25	0	0	0	0
	50	5	12.5	13	0.08
3.1	10	1	2.5	1	0.01
	25	1	2.5	1	0.01
	50	2	5.0	2	0.01
3.2	10	0	0	0	0
	25	1	2.5	1	0.01
	50	2	5.0	3	0.02
3.3	0	0	0	0	0

An improvement of spray quality at lower pH values (pH 2.7-3.0) in combination with lower NaEDTA concentrations (10 and 25 mg) is observed. Formulations with 10 and 25 mg Na EDTA in pH range of 2.7 to 3.2 show not more than 0.1% of all actuations to be classified as sprays with deviations from the typical spray pattern.